Part I

Basic Hematology Principles

WORD KEY

Acrocyanosis • Blue or purple mottled discoloration of the fingers, toes, and/or nose

Angina pectoris • Oppressive pain or pressure in the chest

Chemotherapy • Drug therapy used to treat infections, cancers, and other diseases

Dyspnea • Shortness of breath

Hepatosplenomegaly • Enlargement of liver and spleen

Hypoxia • Decreased oxygen

Myelotoxic • Chemicals that destroy white cells

Palpitation • Sensation of rapid or irregular beating of the heart

Postural hypotension • Change in blood pressure from sitting to standing

RES system • Reticuloendothelial system, the mononuclear phagocytic system

Syncope • Fainting

Tachycardia • Fast and hard heartbeat

Anaerobic • Able to live without oxygen

Asynchrony • Failure of event to occur at the same time

Cytoskeleton • Internal structural framework of the cell

Disseminated intravascular coagulation • Pathological condition in which the coagulation pathways are hyperstimulated, either excessive fibrin disposition or excess fibrinolysis

Pathology • Study of the nature and cause of disease which involved changes in structure and function

Splenectomy • Removal of the spleen

Thrombi • Plural of thrombus; a blood clot that obstructs a blood vessel or a cavity of the heart

Acidosis • Increase in the acidity of blood (as in diabetic acidosis) due to an excessive loss of bicarbonate (as in renal disease)

Alkalosis • Increase in blood alkalinity due to an accumulation of alkaline or reduction in acid

Allosteric • Shape change

Amino acid • One of a large group of organic compounds marked by the presence of both an amino group (NH_2) and a carboxyl group (COOH); the building blocks of protein and the end products of protein digestion

Complement • Group of proteins in the blood that play a vital role in the body's immune defenses through a cascade of interaction

Cyanosis • Blue tinge to the extremities (lips, fingers, toes)

Hyperplasia • Excessive proliferation of normal cells in the normal tissue of an organ

Polychromasia • Blue tinge to the red cells indicating premature release

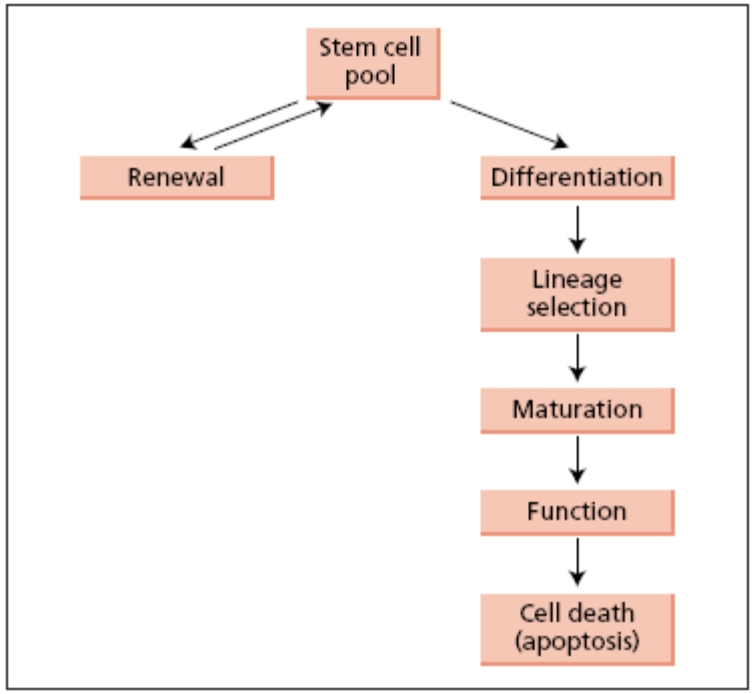


Figure 1.1 Stages in haemopoietic cell development.

Table 1.1 Basic immunophenotype of haemopoietic stem cells.

Positive	*Negative*
CD34	CD33
Thy-1	CD38
AC133	Lineage markers
c-Kit	HLA-DR

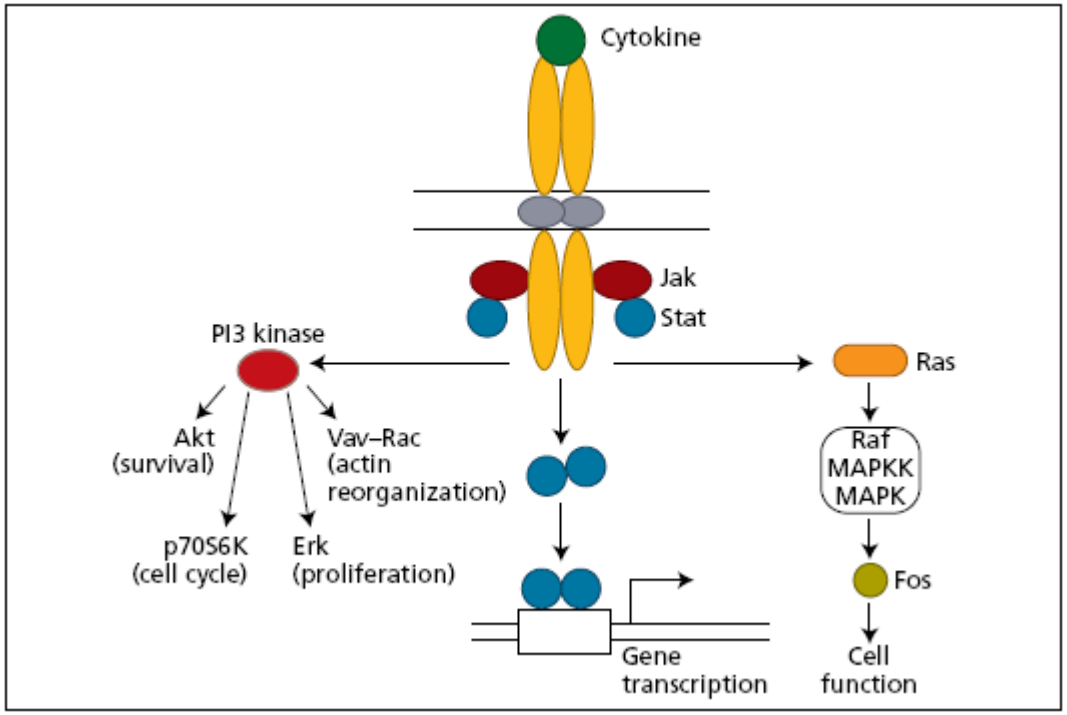
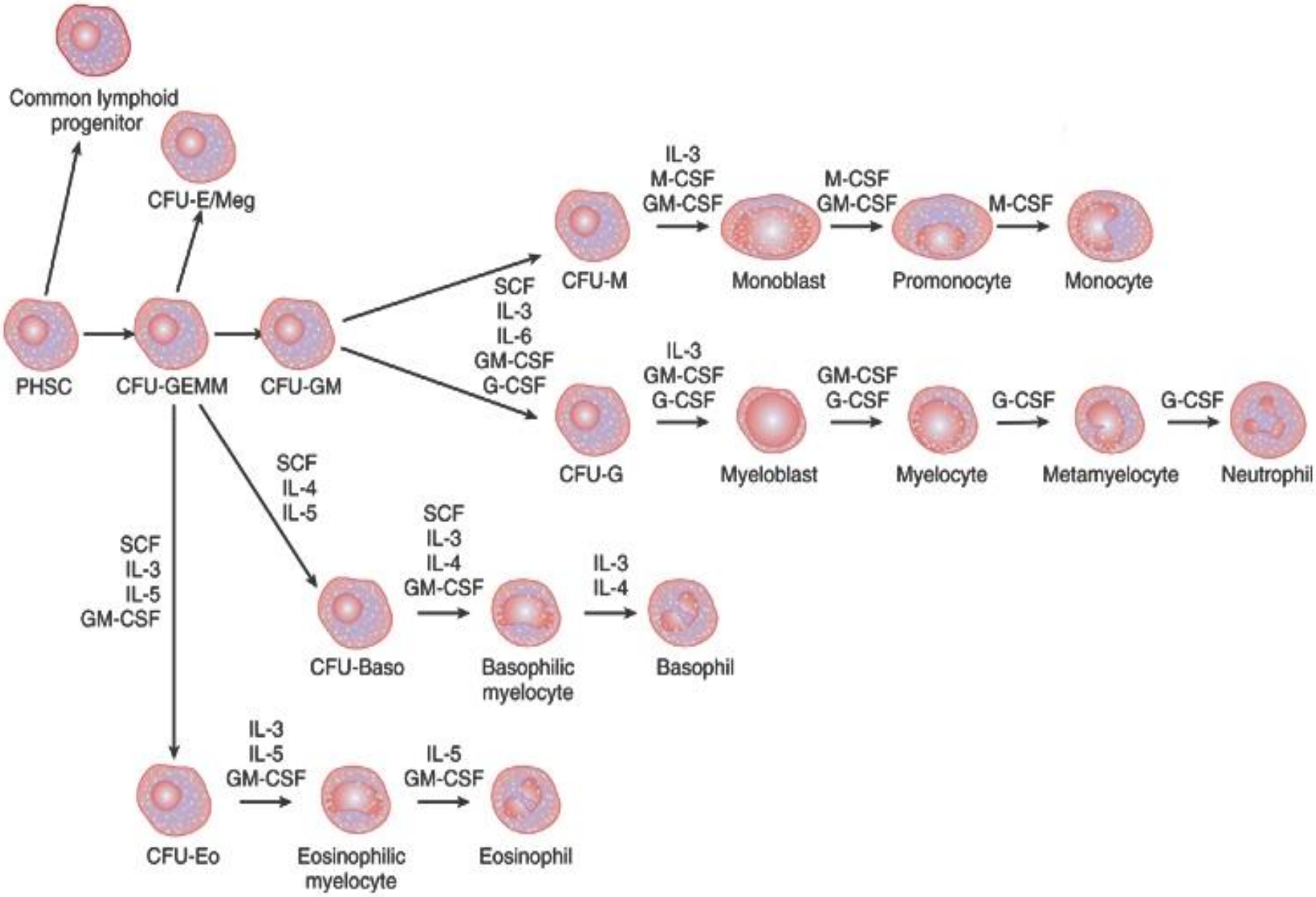


Figure 1.8 Generalized diagram of the signal transduction pathways activated by cytokines and their receptors in haemopoietic cells.



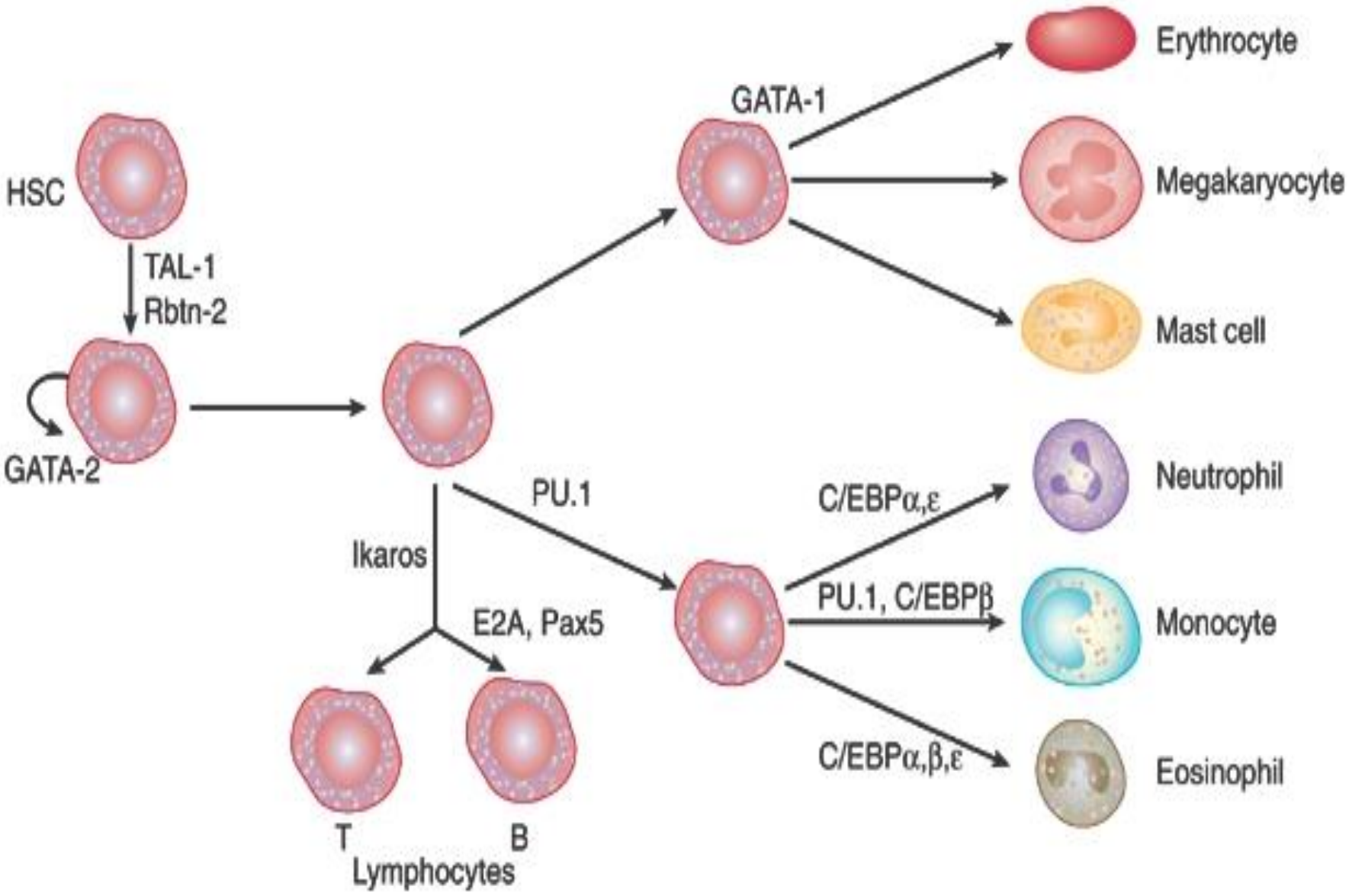
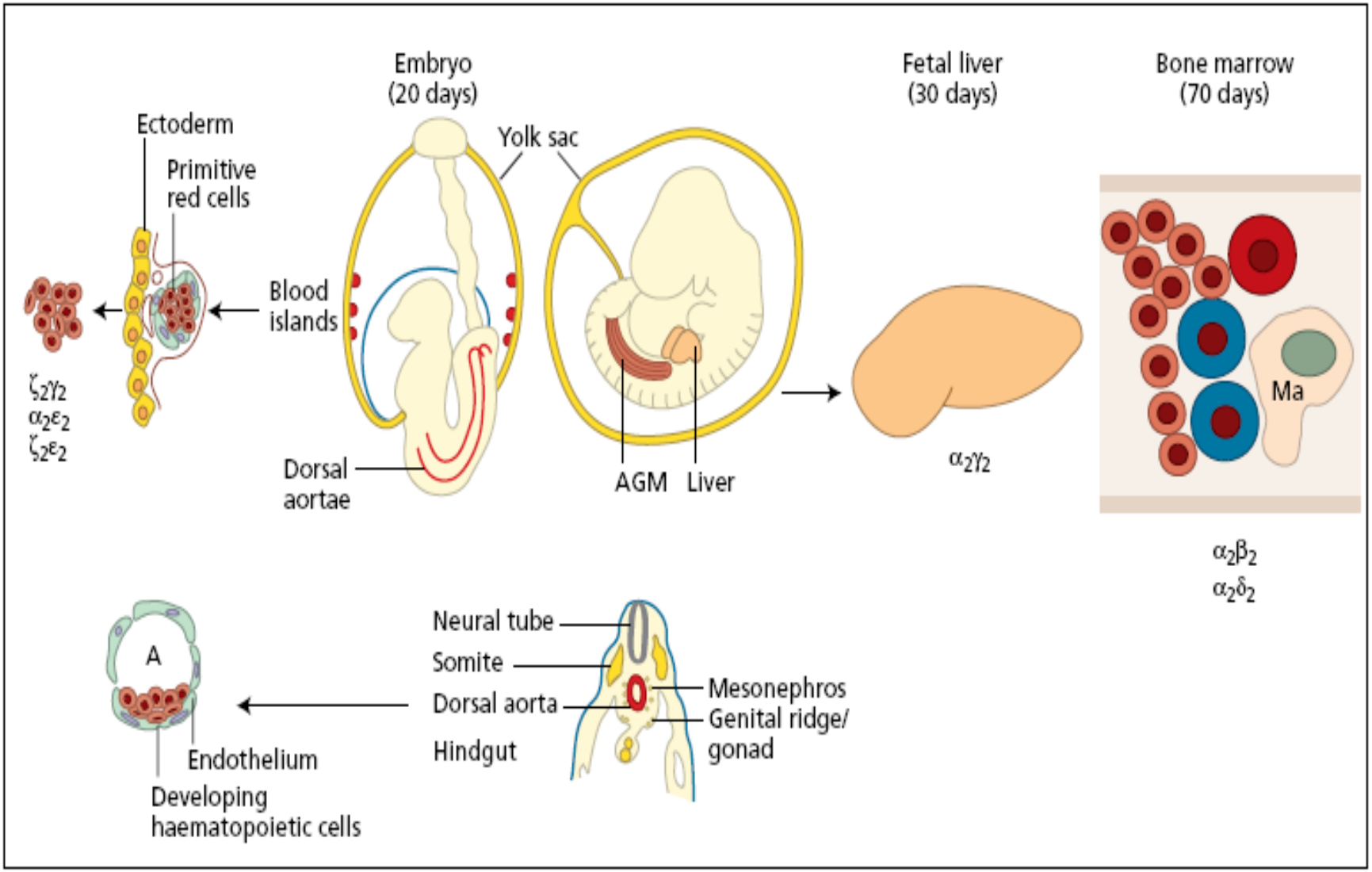


Table 19-2 Redundancy in Cytokine Activities

Hematopoietic Process	Cytokines with Important Enhancing Activity*
Erythropoiesis	Epo, SCF, IGF-1, IL-9, IL-3, Tpo
Megakaryopoiesis	Tpo, IL-3, IL-6, IL-11, LIF, SCF, Epo, SCF
Mast cell formation	IL-3, SCF, IL-10?
Eosinophil formation	IL-5, IL-3, GM-CSF, SCF
Granulopoiesis	G-CSF, GM-CSF, IL-3, SCF, IL-6
Macrophage formation	M-CSF, GM-CSF, IL-3
Lymphocyte production	IL-7, FL, SCF, SDF-1, IL-2, IL-4, IL-5, IL-10, IL-13, IL-15


Embryo
(20 days)
Fetal liver
(30 days)
Bone marrow
(70 days)
Ectoderm
Primitive
red cells
Yolk sac
Blood
islands
Dorsal
aortae
AGM
Liver
Ma
ζ2γ2
α2ε2
ζ2ε2
α2γ2
α2β2
α2δ2
A
Endothelium
Developing
haematopoietic cells
Neural tube
Somite
Dorsal aorta
Hindgut
Mesonephros
Genital ridge/
gonad

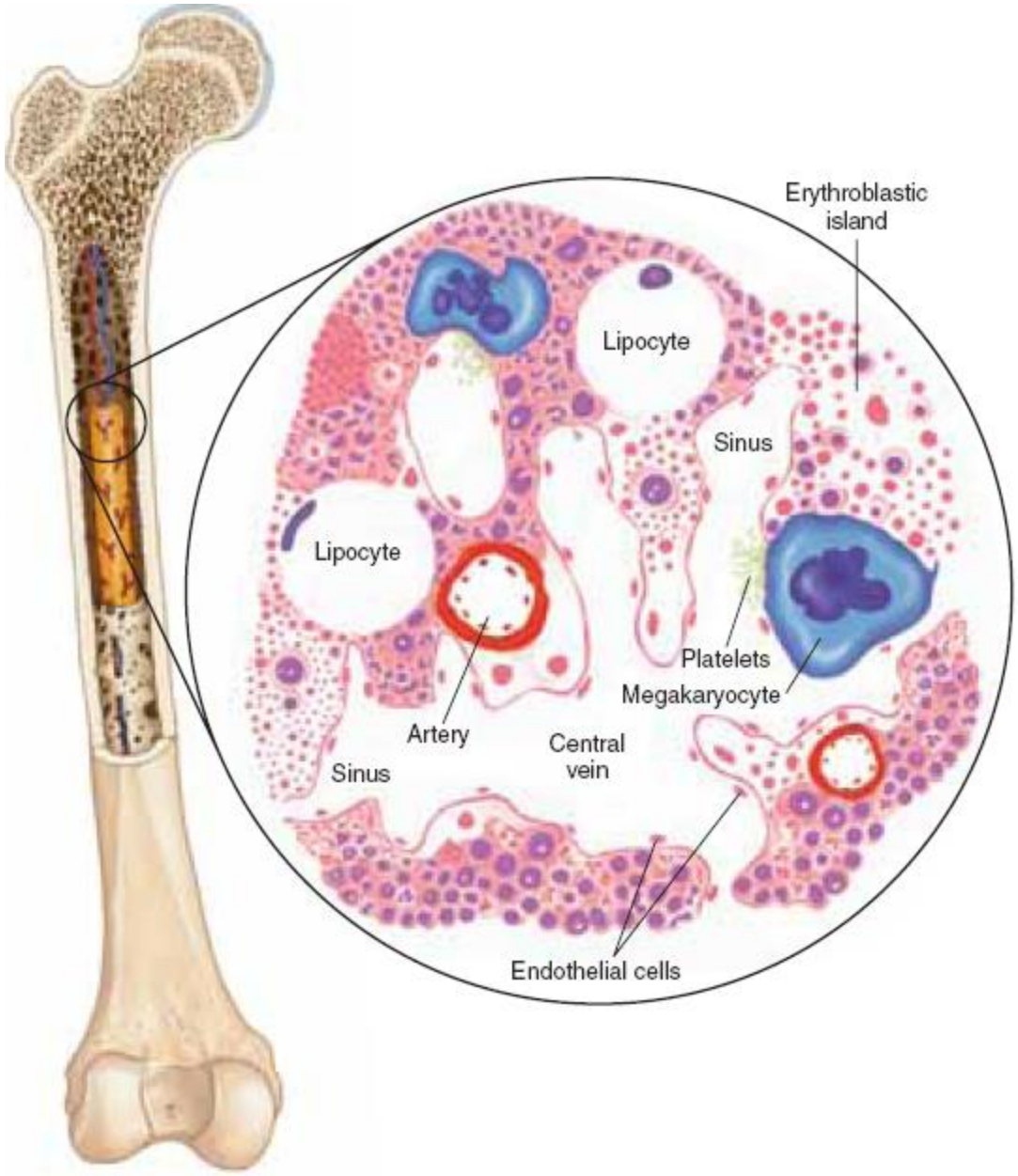


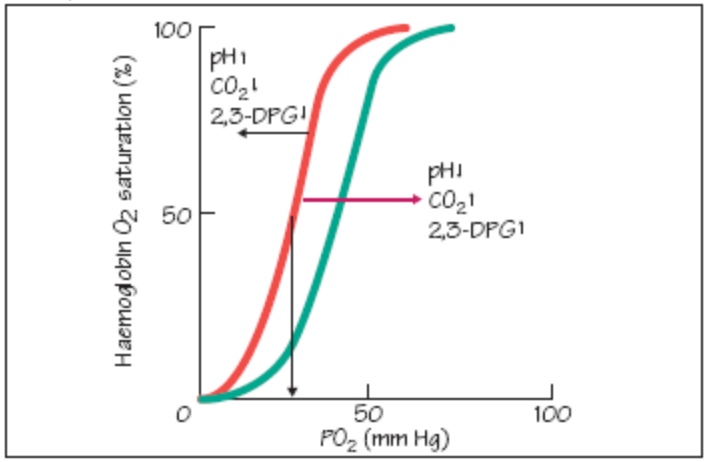
Figure 2.2 Internal structure of the bone marrow.

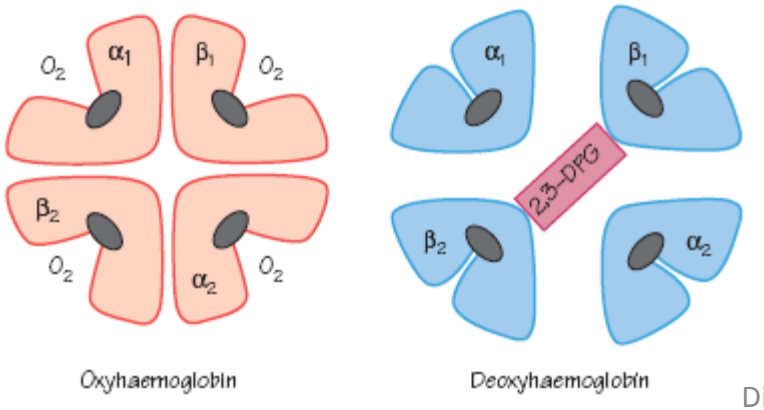
Table 1.1 Haemopoietic growth factors.

Act on stromal cells
IL-1 {Stimulate production of other growth factors}
TNF
Act on pluripotential cells
Stem cell factor
Act on early multipotential cells
IL-3
IL-4
IL-6
GM-CSF
Act on committed progenitor cells*
G-CSF
M-CSF
IL-5 (eosinophil CSF)
Erythropoietin
Thrombopoietin

*These growth factors (especially G-CSF and thrombopoietin) also act on earlier cells.

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, monocyte colony-stimulating factor; TNF, tumour necrosis factor.





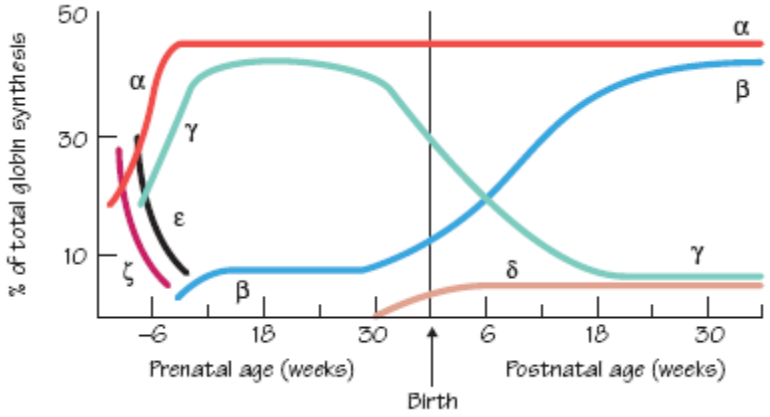
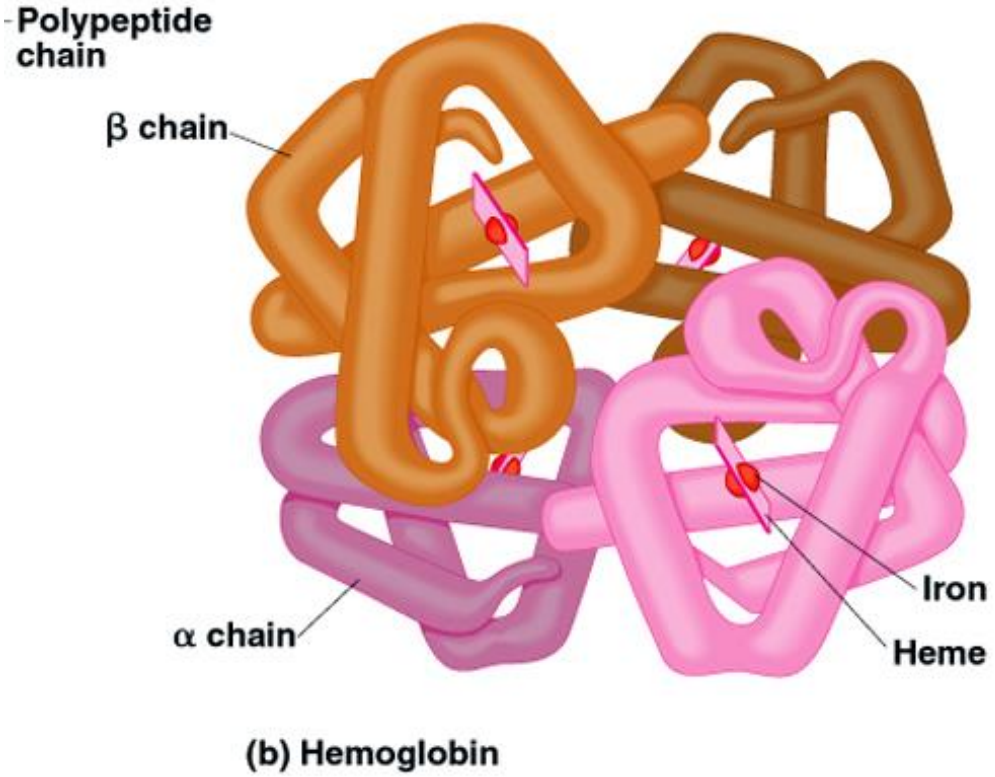
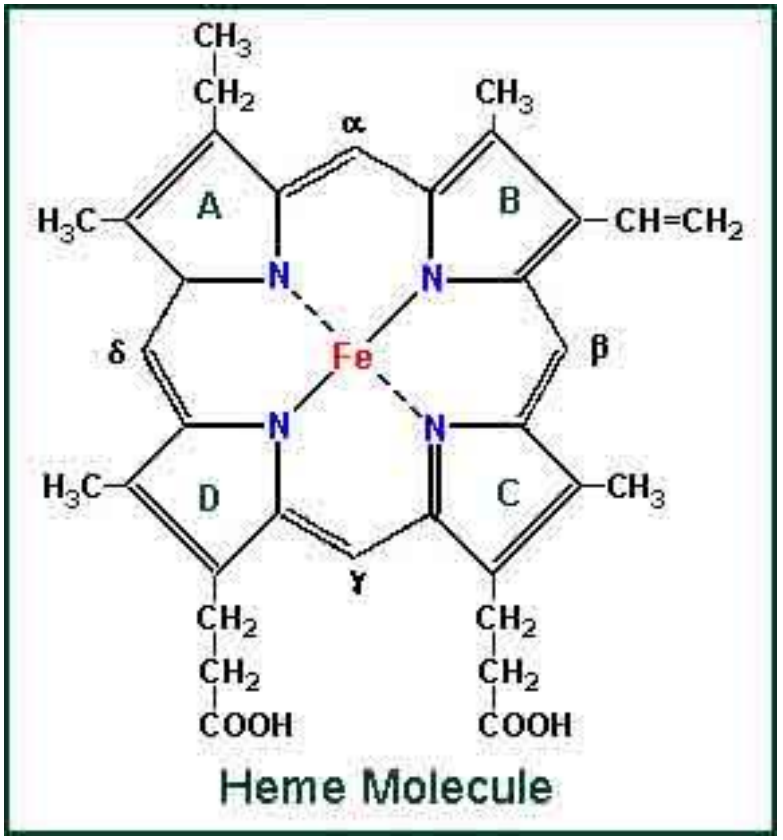


TABLE 14-1 **HUMAN HEMOGLOBINS**

Embryonic Hemoglobins	*Fetal Hemoglobin*	*Adult Hemoglobins*
Gower 1—$zeta_2epsilon_2$ ($\zeta_2\ \varepsilon_2$)	Hemoglobin F—$alpha_2gamma_2$ ($\alpha_2\ \gamma_2$)	Hemoglobin A—$alpha_2beta_2$ ($\alpha_2\ \beta_2$)
Gower 2—$alpha_2epsilon_2$ ($\alpha_2\ \varepsilon_2$)		Hemoglobin A2—$alpha_2delta_2$ ($\alpha_2\ \delta_2$)
Portland—$zeta_2gamma_2$ ($\zeta_2\ \gamma_2$)		



(b) Hemoglobin



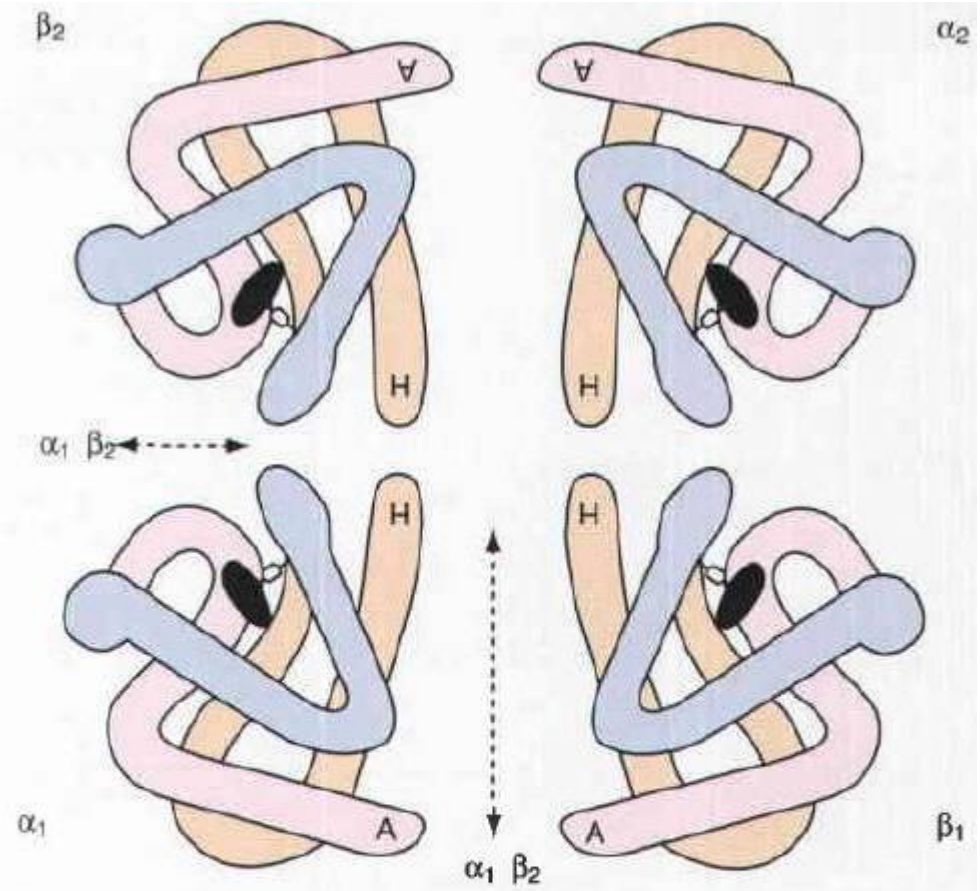


Figure 30–11 The hemoglobin molecule (tetramer, molecular weight 64 500 Da). The heme group for each monomeric polypeptide chain is depicted as a black disk, connected to an imidazole group of histidine, and located near the surface of the molecule in a 'pocket' formed by the polypeptide chain. The letters A and H designate alphahelix segments of each polypeptide chain: A is the amino-terminal segment, and H is the carboxy-terminal segment. The four monomers are separated in this drawing, but actually make contact along a relatively large area ($\alpha_1\beta_1$) which is thought to be the relatively fixed or stabilizing contact area, and a smaller ($\alpha_1\beta_2$) area thought to be the functional contact area, where movement occurs during oxygenation and deoxygenation, changing the molecular configuration. (Redrawn from White JM, Dacie JV: Prog Hematol 1971; 7:69, with permission.)

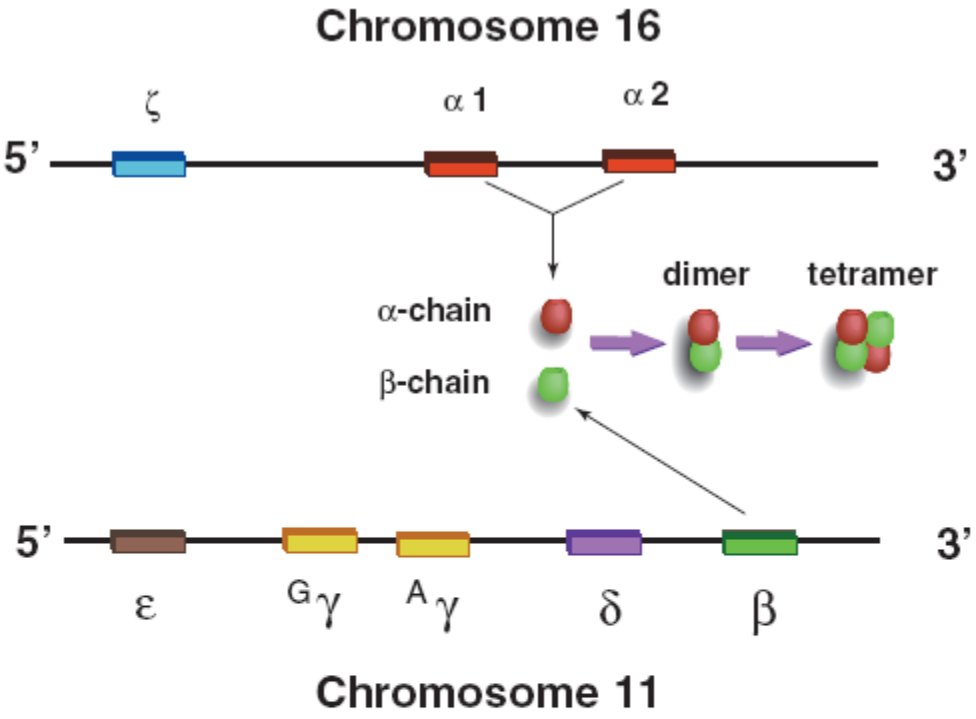


FIGURE 14–1 *Hemoglobin synthesis and assembly. Chromosome 16 is the location of the "α-like" globin gene cluster, while the "β-like" globin gene cluster exists on chromosome 11. The globin genes in each group have internal similarity while differing significantly from their counterparts in the other gene cluster. During development, the globin genes sequentially turn on and off beginning at the 5′ end of the gene cluster. The two α-globin genes on chromosome 16 (α1 and α2) produce the α-globin subunit in adult hemoglobin A. The β-globin gene on chromosome 11 produces the β-globin subunit. The quantity of globin subunit produced by the β-globin gene precisely matches the α-globin subunit production of the two α-globin genes. The individual globin subunits quickly associate to an αβ dimer. The two dimers associate to form an $\alpha_2\beta_2$ tetramer, which is the functional hemoglobin molecule.*

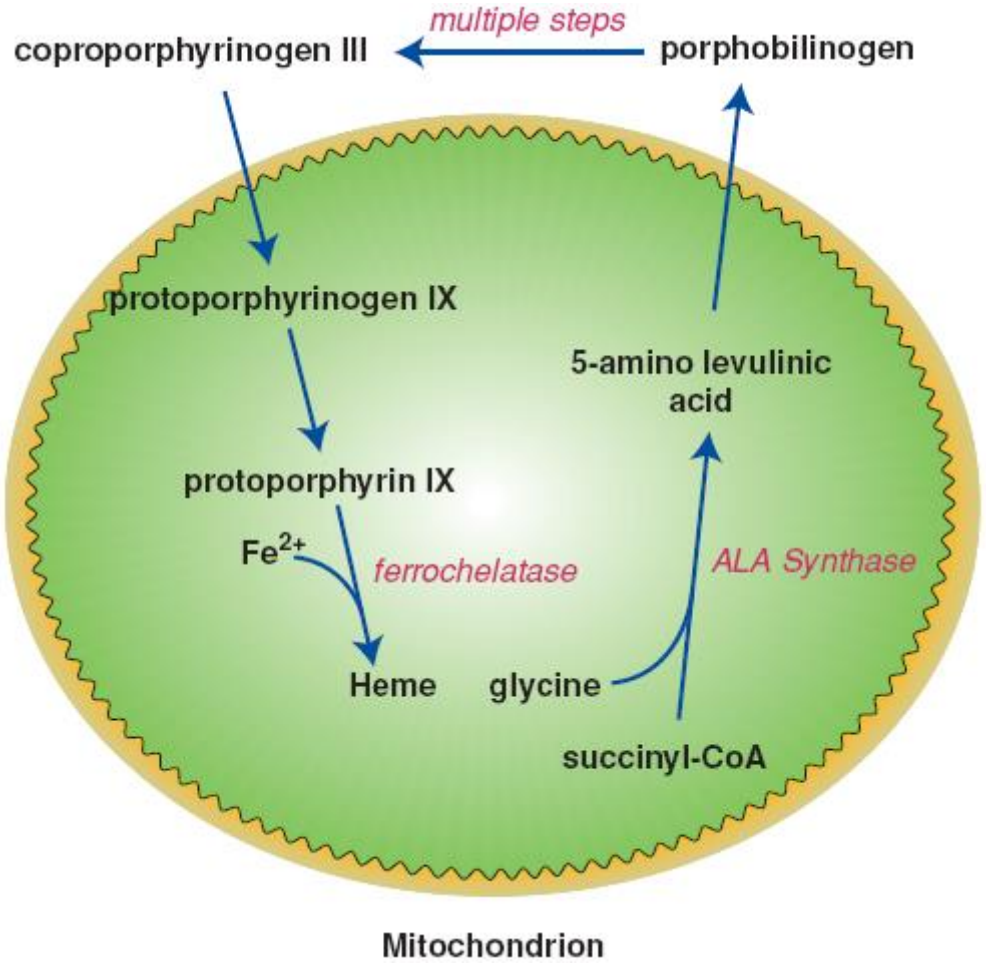


FIGURE 12–2 *Simplified schema of heme biosynthesis. Heme biosynthesis begins in the mitochondrion with the condensation of succinyl-CoA and glycine to form 5-aminolevulinic acid (δ-aminolevulinic acid). Biosynthesis moves to the cytosol where multiple enzymatic steps produce coproporphyrinogen III. This molecule enters the mitochondrion for the final steps of heme biosynthesis.*

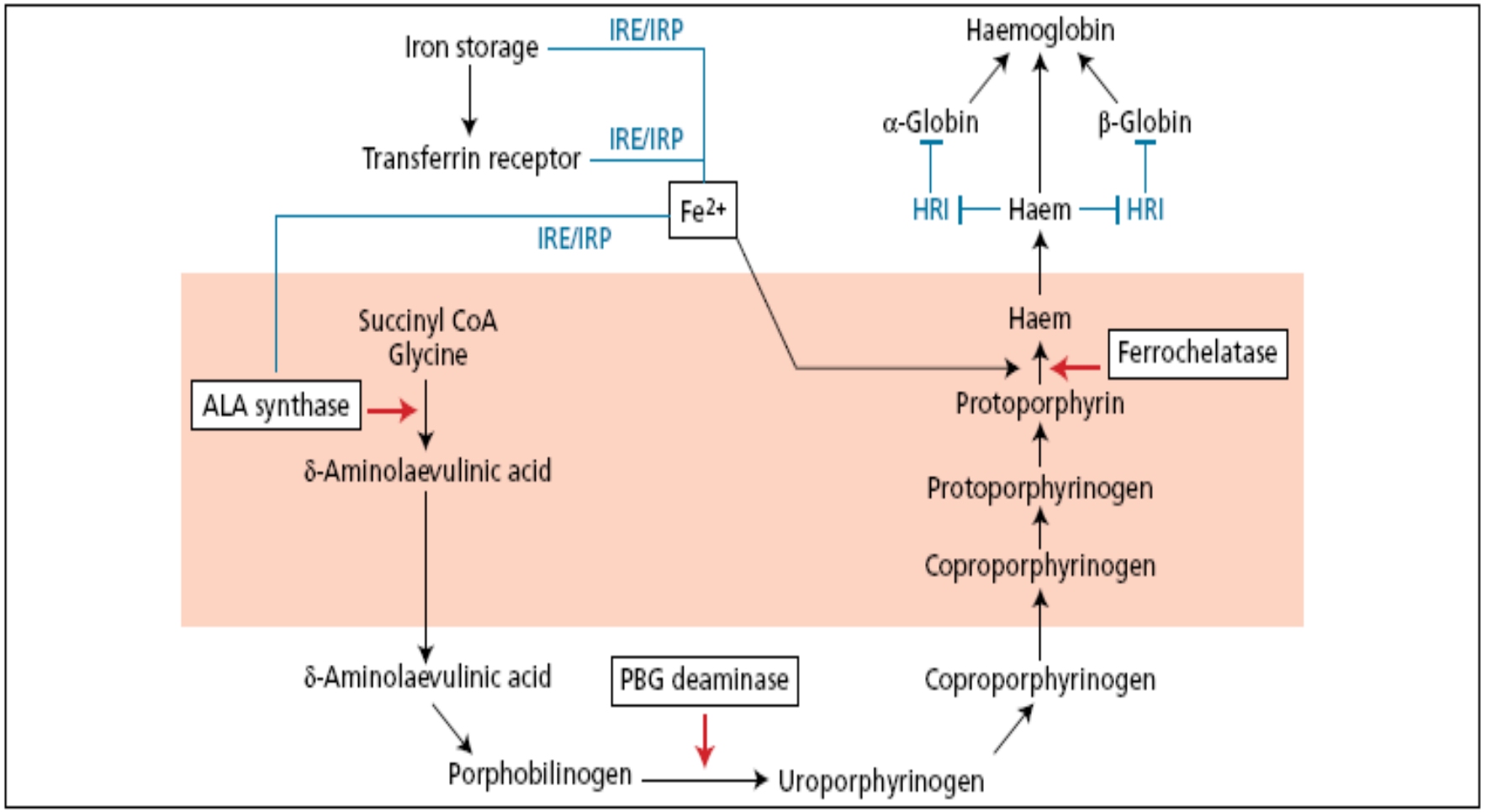


Figure 2.5 The coordination of globin synthesis, haem synthesis and iron regulation. Blue lines indicate some of the known regulatory feedback systems. The red shaded box indicates reactions occurring in the mitochondria. Rate-limiting controls of haem synthesis are shown in black boxes.

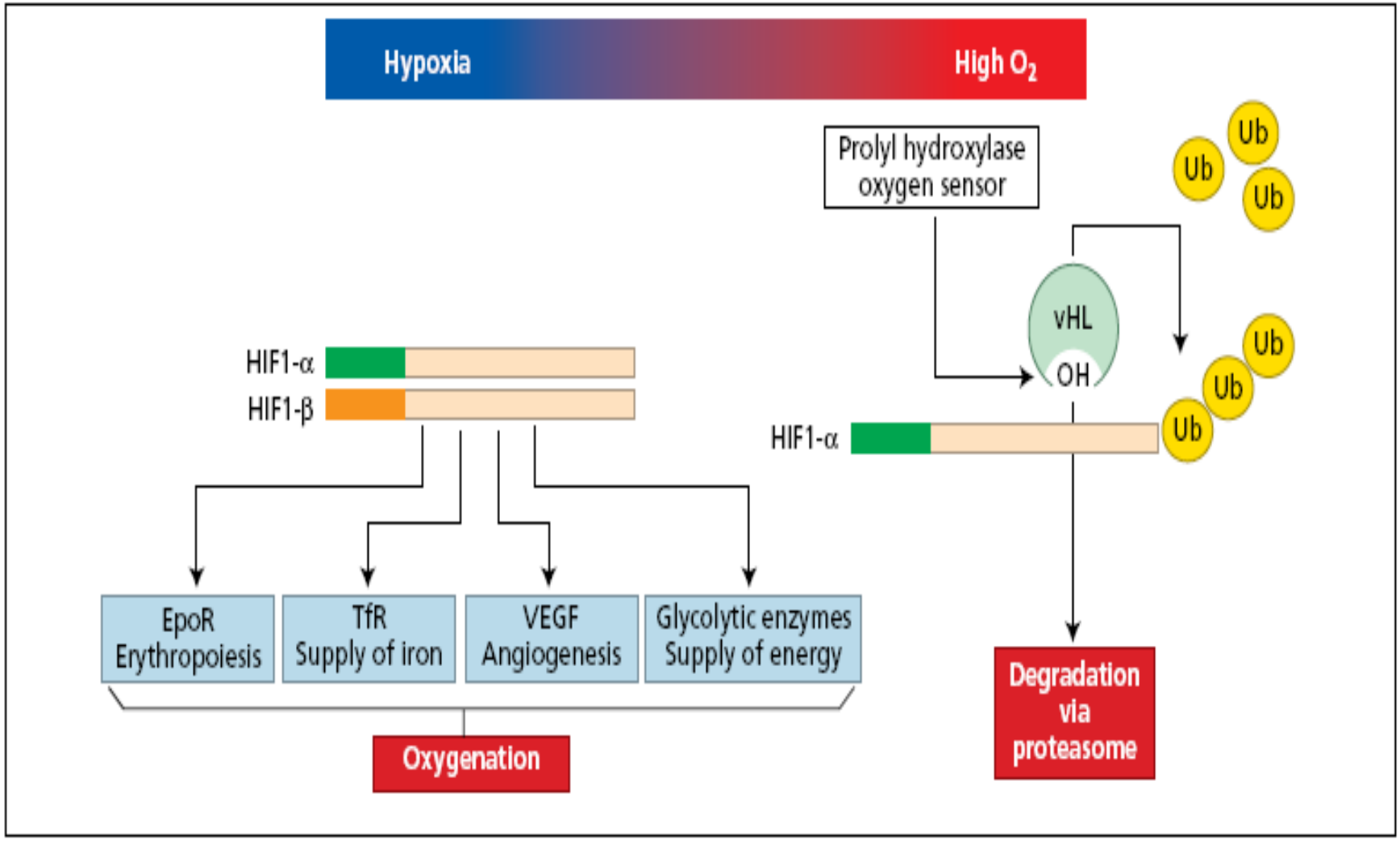
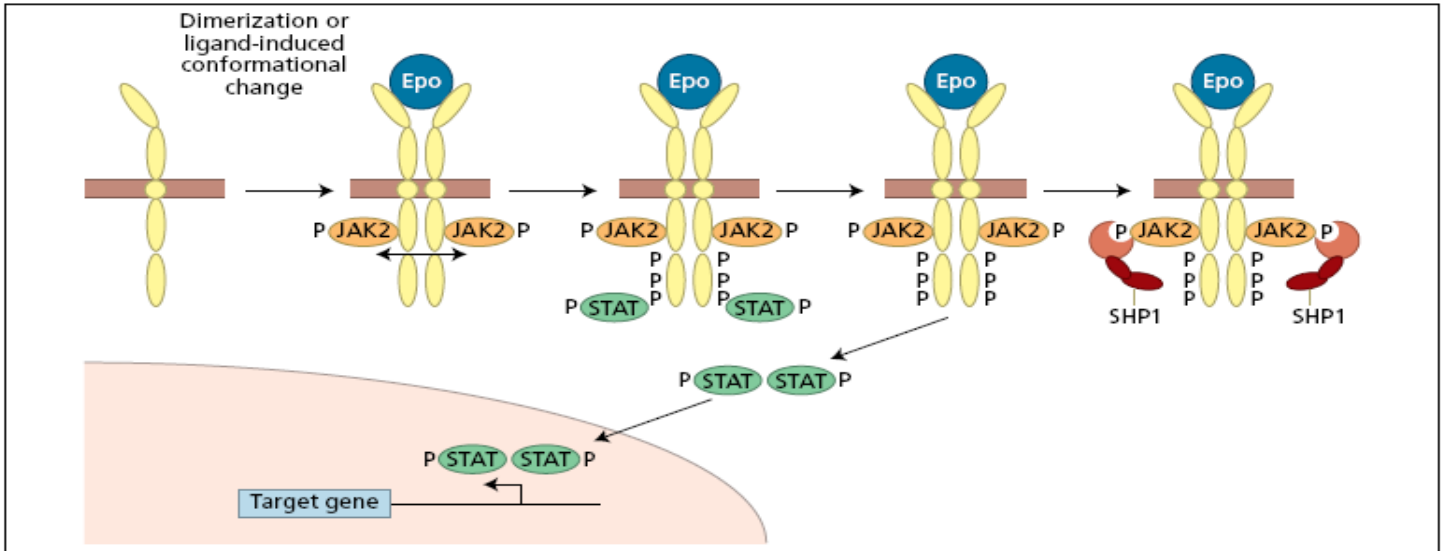
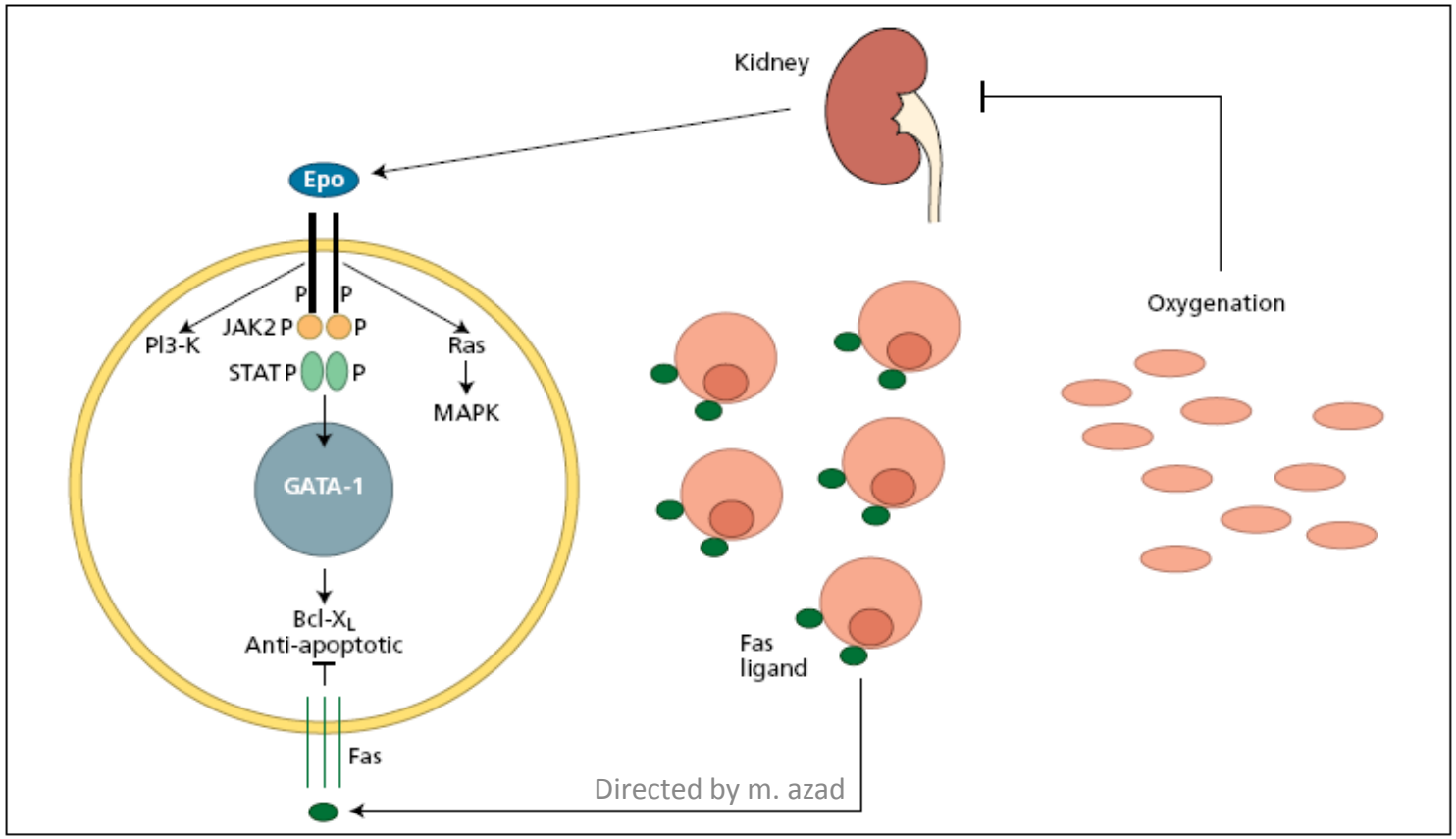


Figure 2.6 The oxygen-sensing system. vHL indicates the von Hippel–Lindau protein. Ub indicates ubiquitination.


Dimerization or ligand-induced conformational change
Epo
JAK2
P
STAT
SHP1
Target gene


Kidney
Epo
PI3-K
JAK2
STAT
Ras
MAPK
GATA-1
Bcl-X$_L$
Anti-apoptotic
Fas
Fas ligand
Oxygenation

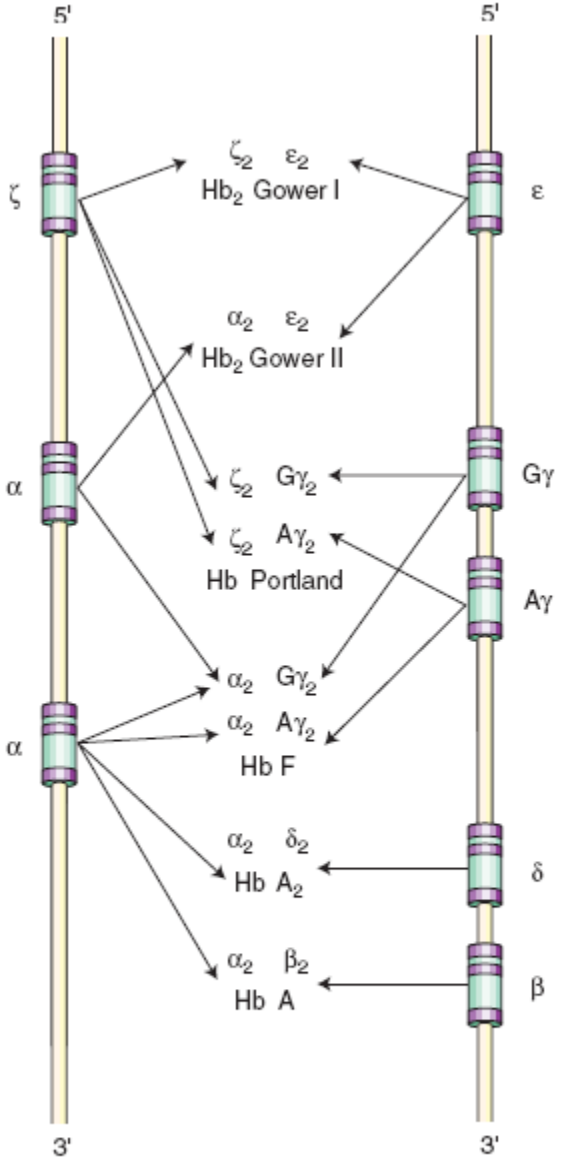
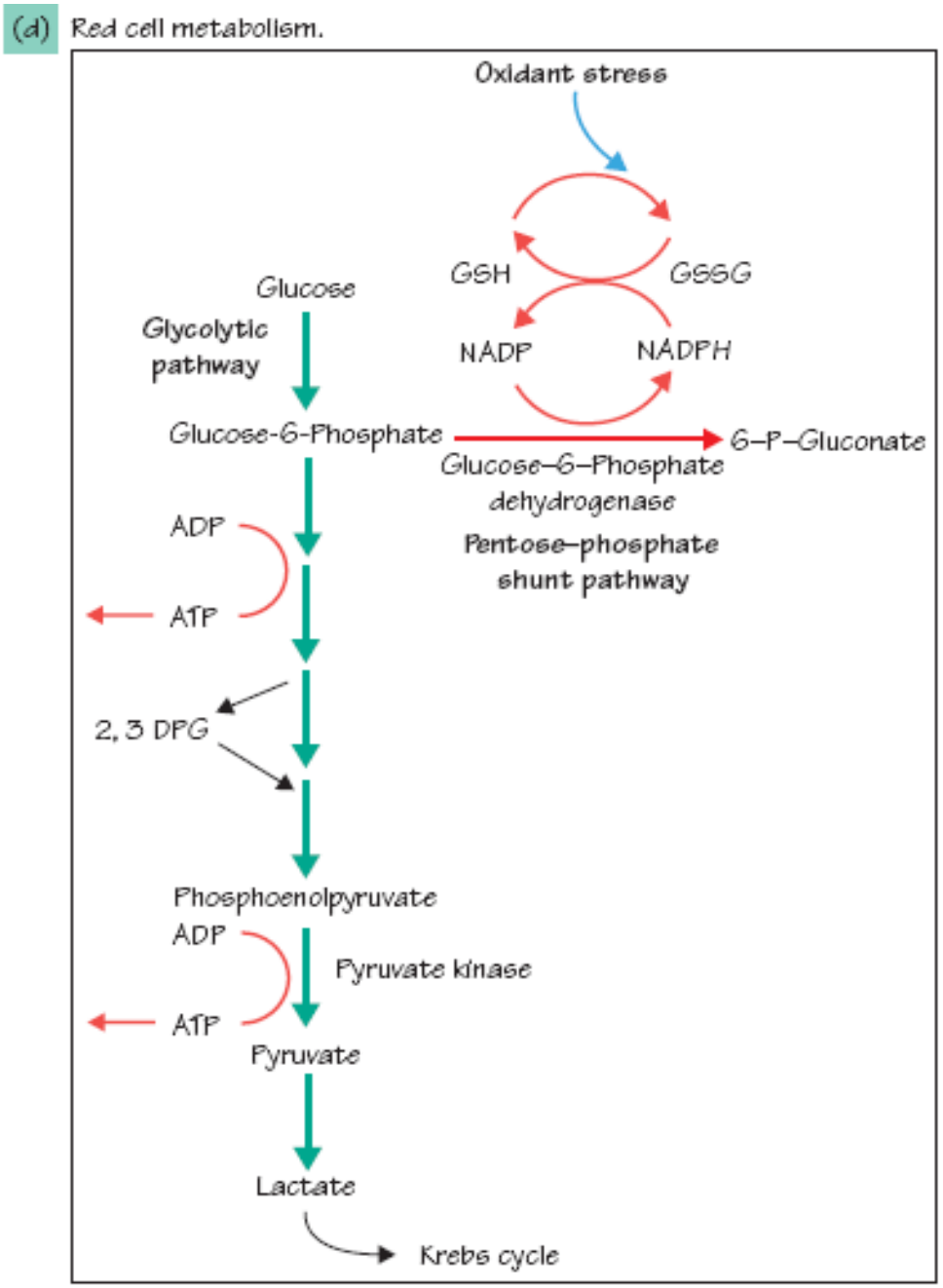
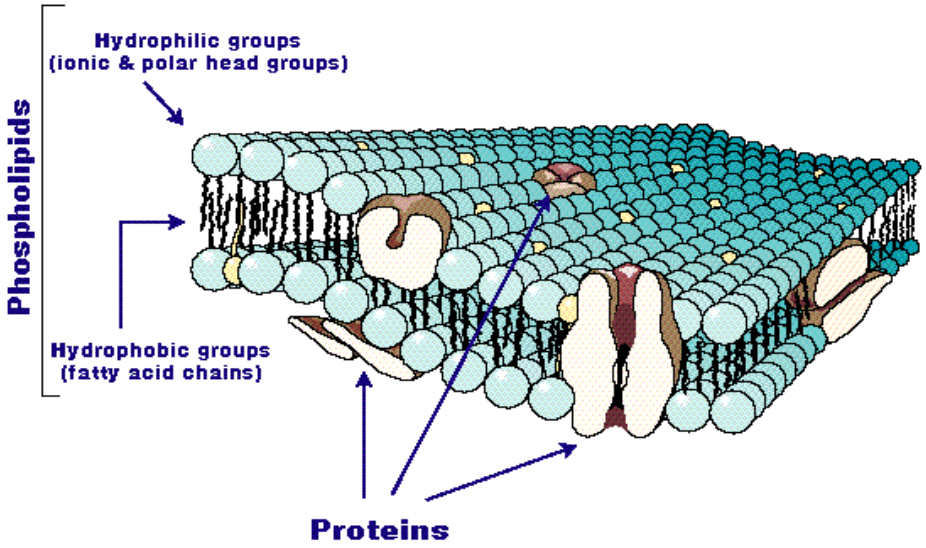


Figure 4.2 Specific chromosomes relative to human hemoglobin formation.



RBC Mambrane



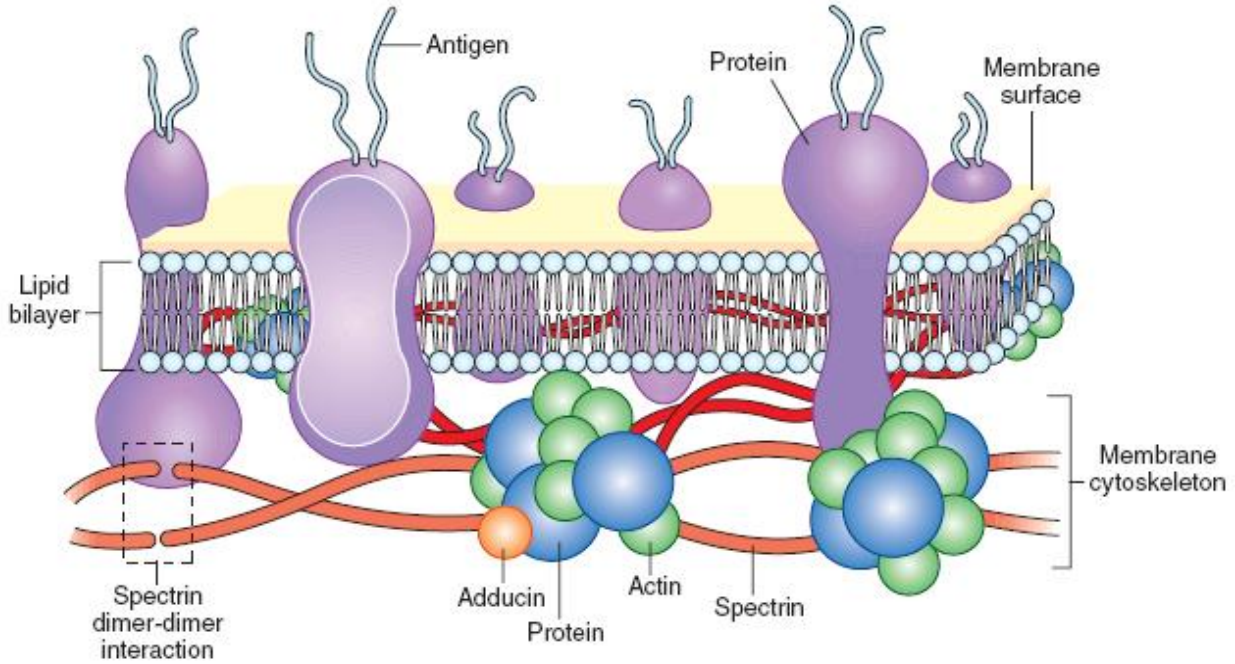


Figure 3.8 Red blood cell membrane. Note placement of integral proteins (glycophorins—in purple) versus peripheral proteins (spectrin, ankyrin).

Fig. 2.1 The interaction of blood cellular elements and proteins with the tissues

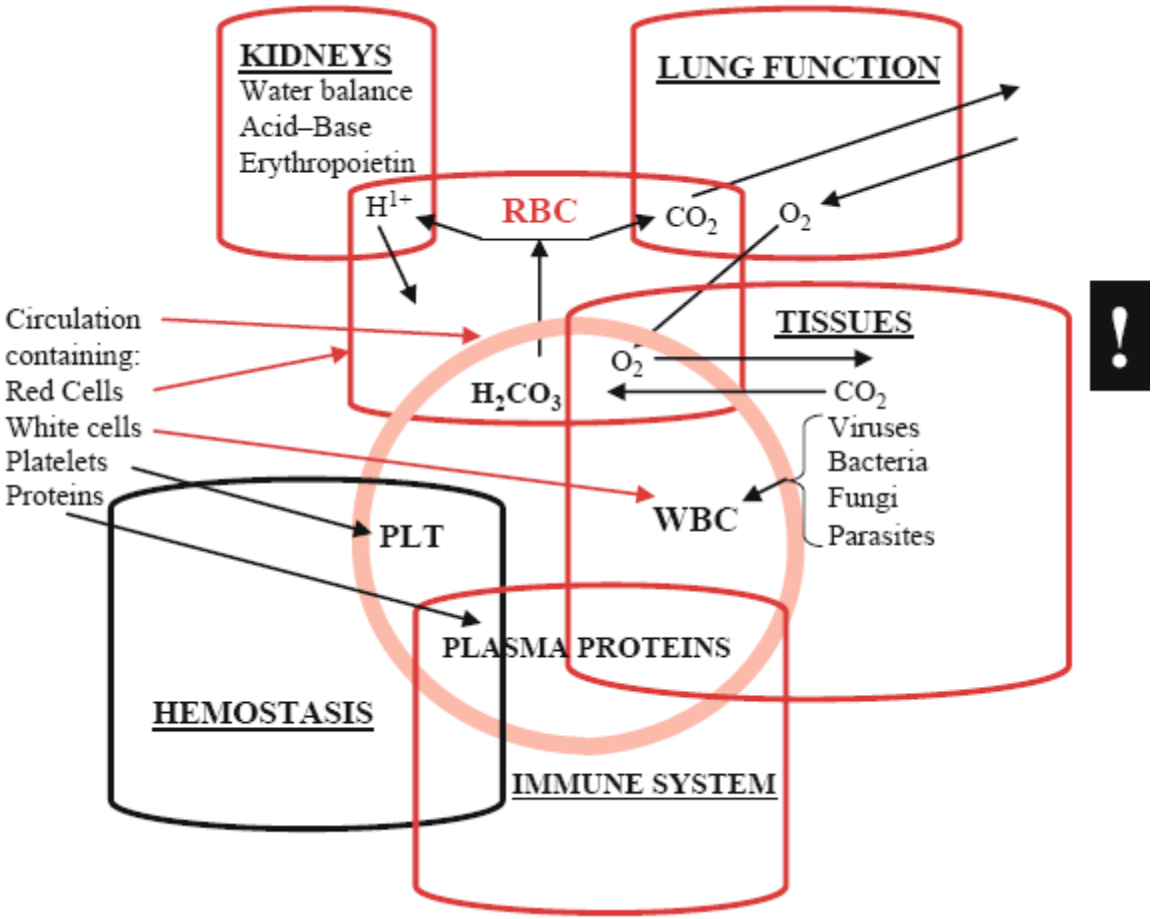


Figure 1–1 Erythrocytes. Note that the size of the erythrocytes is about the same as the nucleus of the small resting lymphocyte.

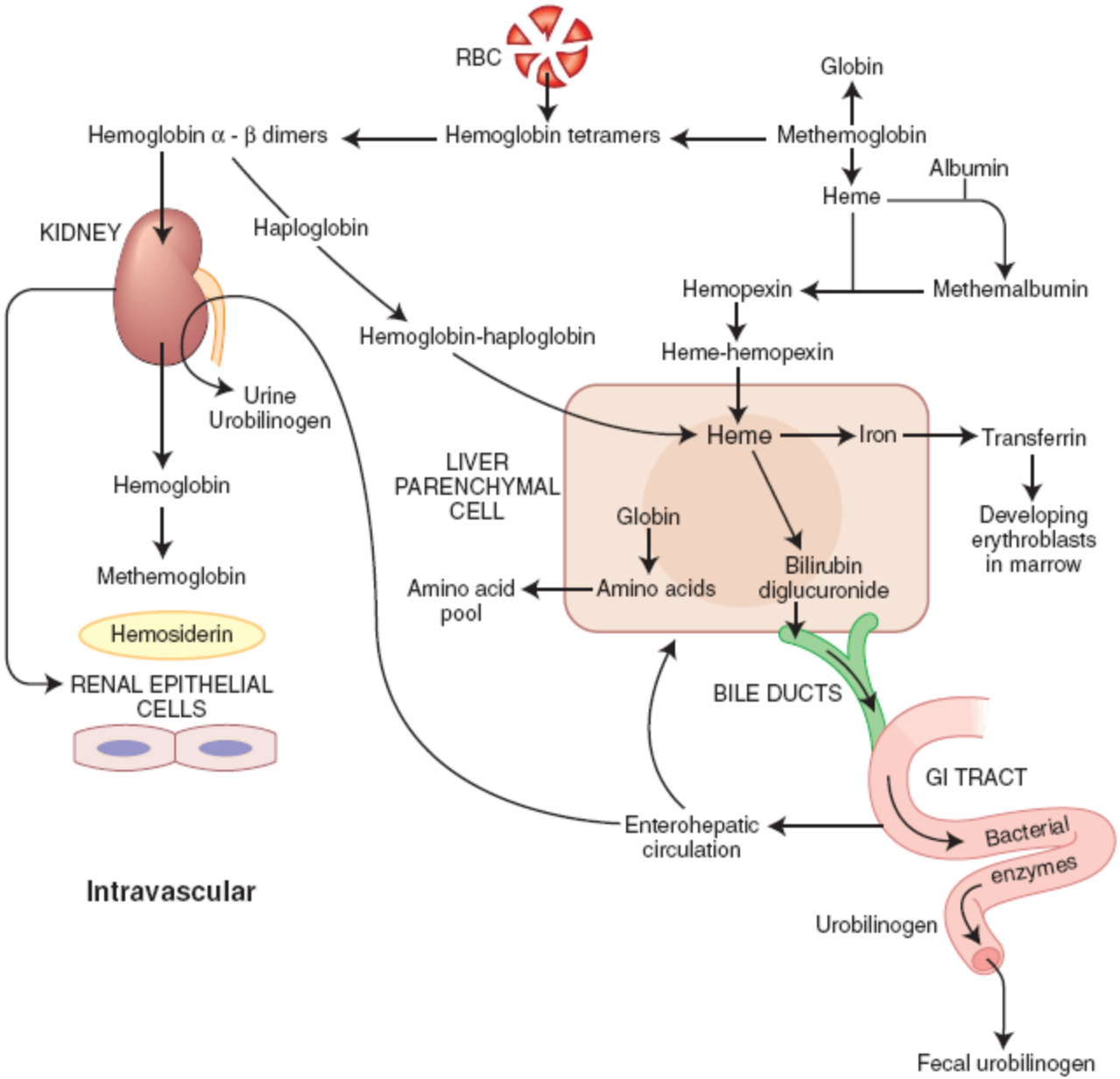


Figure 4.4 Intravascular hemolysis: increased bilirubin, decreased haptoglobin, but free hemoglobin present.

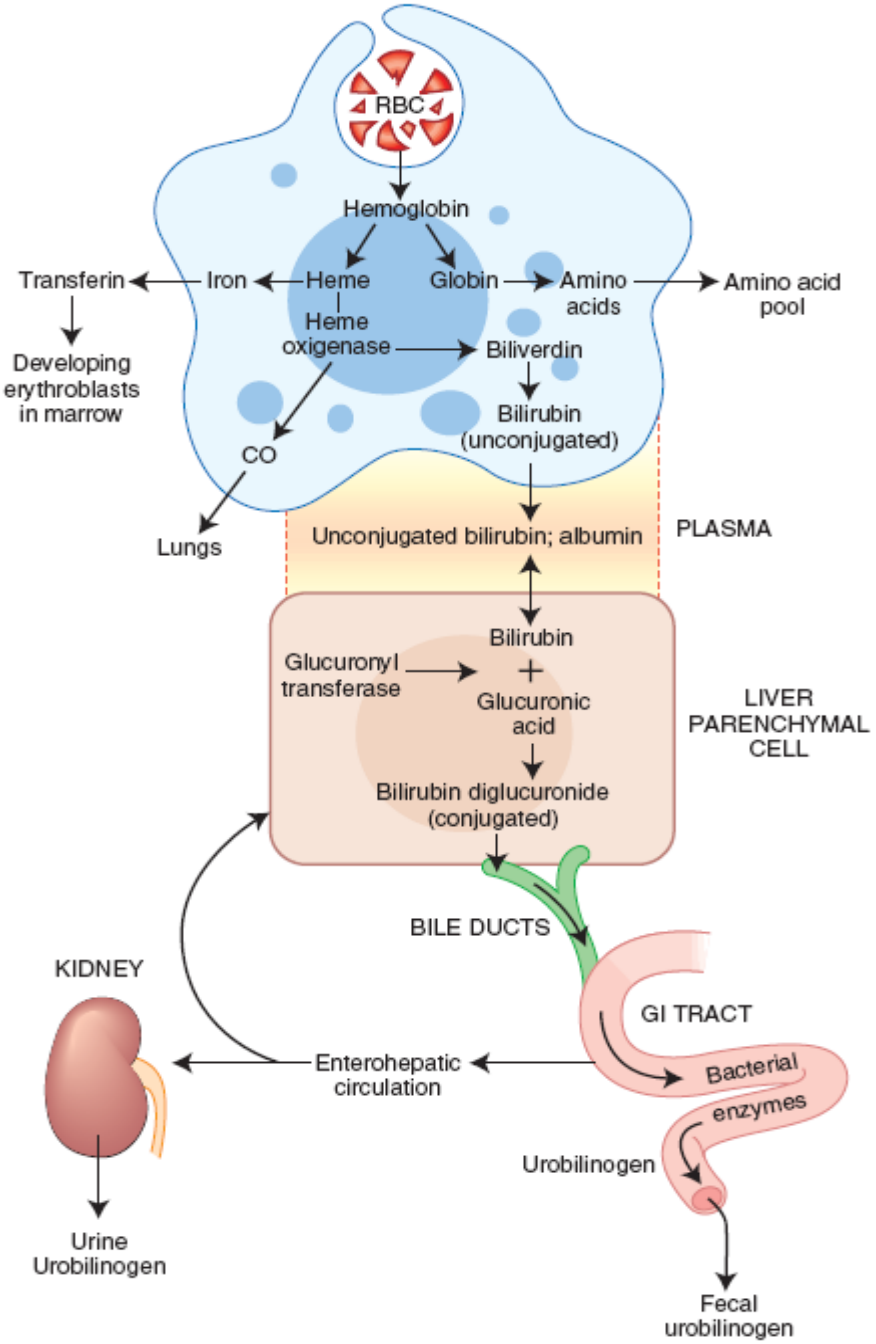


Figure 4.5 Extravascular hemolysis: increased bilirubin and decreased haptoglobin.

Appendix II: cluster of differentiation nomenclature system

Cell surface markers are molecules in the cell membrane that can be recognized by reactivity with specific monoclonal antibodies. Their presence gives information about the lineage, function or stage of development of a particular cell population. The cluster of differentiation (CD) nomenclature system groups together antibodies recognizing the same surface molecule (antigen).

T-cell markers

CD no.	Remarks
1a, b, c	Thymocytes, Langerhans' cells (CD1a)
2	E-rosette receptor. All T cells
3	T-cell receptor. Mature T cells
4	T helper/inducer subset
5	T cells (aberrantly expressed in B-CLL, mantle cell lymphoma)
7	T cells (aberrantly expressed in some AML)
8	T cytotoxic/suppressor

B-cell markers.

CD no.	Remarks
19	B cells, including early B cells
20	Mature B cells
21	Mature B cells. C3d receptor, EBV receptor
22	B cells
23	Activated B cells
79	B cell antigen receptor
103	Hairy cells
138	Plasma cells

Myeloid and other markers.

CD no.	Remarks
Myeloid markers	
11a, 11b, 11c	Adhesion molecule ligand. Also expressed on some B and T cells and monocytes
13	All mature myeloid cells
33	Myelin-associated protein. Early myeloid cells
61	Early myeloid cells
117	Early myeloid cells
Others	
14	Monocytes, macrophages
25	IL-2 receptor-activated B cells
34	Stem cells
45	Leucocyte common antigen: all haemopoietic cells
56	Natural killer cells
9, 29, 31, 41, 42	Platelet markers
38	Plasma cell marker
71	Red cell precursors
TdT	Terminal deoxynucleotidyl transferase—early B- and T-cell precursors

From Hematopoiesis to the Complete Blood Count

Summary Points

- Hematopoiesis is defined as the production, development, and maturation of all blood cells.
- Erythropoiesis in the fetus takes place in the yolk sac, spleen, and liver.
- Erythropoiesis in the adult takes place primarily in the bone marrow.
- Hematopoiesis within the bone marrow is termed *intramedullary hematopoiesis;* outside the bone marrow, it is termed *extramedullary hematopoiesis.*
- The bone marrow is one of the largest nonsolid organs of the body.
- The M:E ratio (3 to 4:1) reflects the amount of myeloid elements in the bone marrow compared with the erythroid elements in the bone marrow.
- Multipotential stem cells are capable of differentiating into nonlymphoid or lymphoid precursor committed cells.

- EPO is a hormone produced by the kidneys that regulates erythroid production.
- A bone marrow aspirate and biopsy are invasive procedures usually performed at the location of the iliac crest in adults.
- The CBC consists of nine parameters: WBC, RBC, Hgb, Hct, MCV, MCH, MCHC, RDW, and platelet count.
- The MCV is one of the most stable CBC parameters over time.
- Increases in MCV can occur as a result of transfusion, reticulocytosis, hyperglycemia, and methotrexate.
- The RDW may be an early indicator of an anemic process.
- Critical values are those that are outside the reference range and that need to be immediately reported and acted on.
- The reticulocyte count is the most effective means of assessing red cell regeneration in response to anemic stress.
- Red cell production is effective when the bone marrow responds to anemic stress by producing an increased number of reticulocytes and nucleated red cells.
- Ineffective red cell production is described as death of red cell precursors in the bone marrow before they can be delivered to the peripheral circulation.
- Morphological classification of anemias is determined by the red cell indices.
- Microcytic, hypochromic anemias are characterized by an MCV of less than 80 fL and an MCHC of less than 32%.
- Macrocytic, normochromic anemias are characterized by an MCV of greater than 100 fL.
- Normocytic, normochromic anemias are characterized by an MCV between 80 and 100 fL and an MCHC of 32% to 36%.
- Normal red cells are disk-shaped flexible sacs filled with Hgb and having a size of 6 to 8 μm.

Red Blood Cell Production, Function, and Relevant Red Cell Morphology

Summary Points

- Red cell production is under the control of erythropoietin (EPO), a hormone released from the kidney
- The main sites of adult erythropoiesis are the sternum and iliac crest.
- Each pronormoblast produces 16 mature red cells.
- As they mature, red cells decrease in size, become less basophilic in their cytoplasm, develop the orange tinge of hemoglobin, and lose their nucleus.
- Another name for an orthochromic normoblast is a nucleated red blood cell (nRBC).
- The red cell membrane is a trilaminar structure containing glycolipids, glycoproteins, cholesterol, and proteins that anchor the cell and provide deformability such as spectrin and ankyrin.
- Integral proteins start from the cytoskeleton and expand through the entire red cell membrane.

- Peripheral proteins are confined to the red cell cytoskeleton.
- Sodium and potassium migrate from the plasma across the red cell membranes in an organized fashion controlled by cationic pumps.
- Deformability and elasticity are crucial properties of the red cell membrane, which must be able to extend is surface area up to 117% to accommodate its passage through arterioles and capillary space.
- The Embden-Meyerhof pathway provides 90% of cellular ATP necessary for anaerobic red cell metabolism.
- Microcytes and macrocytes represent size changes in the red cells determined by abnormal pathologies.
- Microcytes are seen in iron deficiency anemia, thalassemic conditions, iron loading processes, and, in some individuals, with the anemia of inflammation.
- Macrocytes are associated with megaloblastic processes, liver disease, and high reticulocyte counts.
- Polychromasia is the peripheral cell response to accelerated erythropoiesis.
- Hypochromia is a color variation in the red cell determined by lack of hemoglobin synthesis.
- Sickle cells are observed when hemoglobin S is part of the hemoglobin component; there are two types of sickle cells: irreversible or reversible or oat-shaped sickle cells.
- Spherocytes are seen in hereditary spherocytosis, in autoimmune hemolytic anemias, or as a part of red cell senescence.
- Target cells are seen in any condition affecting hemoglobin function and also in liver disease or other processes where cholesterol is loaded in the circulation.
- Fragmented cells occur as a result of membrane loss and may be seen in heart valve disease, in burns, or in conditions where there is a predisposition of thrombi.
- Ovalocytes can be seen in thalassemic processes and in the megaloblastic anemias where macro-ovalocytes are seen.
- Elliptocytes are seen in iron deficiency anemia, hereditary elliptocytosis, and idiopathic myelofibrosis.
- Howell-Jolly bodies are DNA in origin and seen in conditions of accelerated erythropoiesis: basophilic stippling is RNA in origin and is seen in lead poisoning and accelerated erythropoiesis.
- Heinz bodies are formed from denatured hemoglobin, usually from individuals with glucose-6-phosphate dehydrogenase deficiency.
- Pappenheimer bodies/siderotic granules are iron in origin and seen in iron loading process or in patients who are hypertransfused.

Hemoglobin Function and Principles of Hemolysis

Summary Points

- Hemoglobin has two main components: heme and globin.
- Heme consists of iron and the protoporphyrin ring.
- Globin consists of amino acid chains of specific lengths and specific amino acids; alpha and beta chains are the two most significant amino acid chains.
- Alpha chains have 141 amino acids, and beta chains have 146 amino acids.
- Hemoglobins Gower and Portland are embryonic hemoglobins; hemoglobin F is fetal hemoglobin, and the adult hemoglobins are hemoglobins A, A_2, and F.
- Oxygen delivery is the primary purpose of the hemoglobin molecule.
- 2,3-DPG is intimately related to the oxygen affinity of hemoglobin.
- The OD curve schematically represents the saturation of hemoglobin with oxygen and the release of oxygen from the hemoglobin molecule under normal and abnormal physiological conditions.
- Hemolysis is the premature destruction of the red cell before its 120-day life cycle.
- Hemolysis may be classified as intravascular or extravascular, which relates to the site of hemolysis.
- Intravascular hemolysis takes place inside the blood vessels; extravascular hemolysis takes place outside the blood vessels, primarily in the RES system.
- Hemolytic anemias may be classified by intrinsic defects of the red cell or extrinsic defects that affect the red cell.

پایان